40 NICOTINE INCREASES THE FIRING RATE OF VENTRAL TEGMENTAL AREA NEURONS *IN VITRO*

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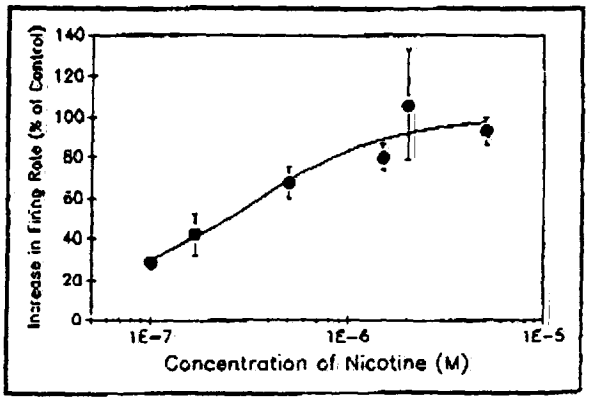
The ventral tegmental area of Tsai (VTA) contains a high concentration of dopamine-containing neurons, and has been implicated in the rewarding properties of drugs of abuse. Central dopamine systems, especially the mesolimbic and mesocortical pathways emerging from the VTA, have been shown to be important in the mediation of the rewarding effects of cocaine, amphetamine, opiates, and alcohol. Recent studies also suggest that mesencephalic dopamine neurons play an important role in the rewarding properties of nicotine. The action of drugs on VTA neurons can be studied with electrophysiological techniques *in vivo* but these studies are subject to a variety of limitations. Using a brain slice preparation of the VTA, neurons can be studied in a controlled environment: known concentrations of drugs can be applied, and the ionic and chemical environment outside of the slice can be precisely manipulated. I have used the brain slice technique to study the effects of nicotine on neuronal activity in a brain slice preparation.

Sprague-Dawley rats (male, 75-125 gm) were used in this study. For each experiment, a rat was sacrificed, its brain removed from the cranium, a block of tissue containing the VTA was prepared on ice, and a 400 μm coronal slice was obtained. This slice was placed in a recording chamber, and was superfused with artificial cerebrospinal fluid at a rate of 2 ml/min. Drugs were added to the superfusion medium via calibrated syringe pumps. Extracellular recordings of spontaneous firing rate over 10 sec intervals was recorded on a chart recorder; firing rate information was also recorded on an IBM-PC-based system for off-line analysis. Units were studied which conformed to electrophysiological parameters established for putative dopamine neurons (Brodie and Dunwiddie, *Brain Research* 425: 106-113, 1987).

Nicotine potently increased the firing rate of all neurons studied. Firing rate was increased up to 300% of basal firing rate. Increases in firing rate were apparent with the administration of concentrations of nicotine as low as 50 nM. With the administration of concentrations of nicotine up to 10 μM, desensitization to the excitatory effects of nicotine was not observed. The concentration-response curve for concentrations from 100 nM to 10 μM yielded an EC50 of about 250 nM. The excitatory effect of nicotine was completely blocked by hexamethonium, but was not altered by atropine. Acetylcholine also increased the firing of VTA neurons; this excitation was potentiated by a low concentration (200 nM) of physostigmine. Higher concentrations of physostigmine (2-10 μM) alone produced excitation, suggesting a tonic release of ACh in this brain slice preparation. The excitatory action of acetylcholine is not completely blocked by hexamethonium, but is blocked by a combination of atropine and hexamethonium, suggesting that both muscarinic and nicotinic receptors are found on VTA neurons.



These studies demonstrate that neurons of the VTA studies *in vitro* are activated by low concentrations of nicotine. Calabresi, *et al.* (*Brit. J. Pharmacol.* 98:135-140, 1989) have recently reported marked desensitization to the excitatory effects of 100 μM nicotine on VTA neurons in a brain slice preparation. By contrast, little or no desensitization was observed in the present studies with concentrations of 100 nM to 10 μM nicotine; therefore, it is possible that desensitization mechanisms are only triggered by very high concentrations of nicotine. Alternatively, only a portion of the nicotine-induced excitation of VTA neurons may be subject to desensitization, and this portion may not be as pronounced at lower concentrations of nicotine as at higher ones. Using concentrations below 10 μM, nicotine excites VTA neurons in a reversible, concentration-dependent manner.

The VTA slice preparation may become a useful tool for the study of agents which can alter the action of nicotine on central neural pathways involved in reward. The abuse of nicotine-containing agents may stem from the effects of nicotine on neurons of the VTA. Through the use of model systems like the VTA slice preparation, pharmacotherapy useful in smoking cessation treatment programs may be developed.

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